AMENDMENTS TO THE SPECIFICATION

Please replace the paragraph on page 11, lines 18-20, with the following paragraph:

Figure 9 demonstrates: (A) that βTrCP~~, a human homolog of Cdc4p,~~ is a short-lived protein when expressed in a mammalian cell; and (B) that human βTrCP is localized to both the nucleus and cytoplasm of HeLa cells.

Please replace the paragraph on page 138, lines 5-24, with the following paragraph:

~~A human homolog of the *S. cerevisiae* Cdc4p,~~ h-βTrCP, was recently identified that targets CD4 for degradation in the presence of the HIV1 viral protein Vpu (Margottin et al., 1998). CD4 proteolysis requires the F-box region of h-βTrCP that interacts with human Skp 1, suggesting that an analogous human SCF machinery operates in the degradation of h-βTrCP substrates (Margottin et al., 1998). Indirect immunofluorescence studies indicated that h-βTrCP was localized both in the nucleus and cytoplasm (Fig. 9), suggesting the possibilities that h-βTrCP can be engineered to target the degradation of mammalian nuclear and cytoplasic proteins. To demonstrate the efficacy of the engineered SCF system in mammalian cells to degrade stable cellular proteins, we studied whether expression of an engineered βTrCP-E7N hybrid is capable of mediating proteolysis of the physiologically stable pRB protein in mammalian cells. βTrCP-E7N and βTrCP-E7N(ΔDLYC) hybrids were constructed in pcDNA3 vector (Invitrogen) and were expressed under the control of the CMV promoter respectively. βTrCP-E7N efficiently interacts with pRB, whereas neither and βTrCP-E7N (ΔDLYC) nor βTrCP itself was capable of associating with pRB in the *in vitro* binding assays (Fig. 10A). The decay of an exogenous HA-tagged pRB protein was then examined in human osteosarcoma Saos-2 cells lacking a functional pRb. As shown in Fig. 10B, pRB was rapidly degraded in Saos-2 cells expressing βTrCP-E7N, but not βTrCP-E7N (ΔDLYC). These results demonstrate that the SCF ubiquitin-proteolytic machinery operates similarly both in yeast and in mammals, and that the F-box-containing ubiquitin-protein ligases can be genetically engineered towards degradation of any cellular proteins of interest.

Please replace the paragraph on page 138, lines 25-32, with the following paragraph:

Figure 9 βTrCP~~, a human homolog of Cdc4p,~~ is an unstable protein localized both in the nucleus and in cytoplasm of Hela cells. **(A)** Human βTrCP is a short-lived protein. The human osteosarcoma Saos-2 cells were transiently transfected with Flag-tagged βTrCP expression plasmid. The decay of F-βTrCP over time were determined by pulse-chase analysis by ^{35}S-Express labeling and immunoprecipitation with the anti-Flag M2 monoclonal antibody at the indicated chase times. **(B)** Hela cells plated on glass coverslips were transfected with Flag-tagged βTrCP (F-TrCP) or control untagged βTrCP. Cellular distribution of the F-TrCP was assayed by indirect immunofluorescence using the anti-Flag M2 monoclonal antibody.